

University of Dundee

The Wee Discovery Book of PDT

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The Wee Discovery Book of PDT

*The Wee Discovery Book of **PDT***

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Chapter 1:

Introduction

Definition: **Wee**

Wee is a Scottish word meaning of small size, i.e. this is a “small” book about PDT

Introduction

The aim of this “wee” book is to give a short overview on photodynamic therapy (PDT) for the skin, for example when used to treat sun damage or skin cancer. PDT can also be used to treat a wide range of cancers and pre-cancers in other organs, from the bowel to the brain.

PDT is unusual as it uses light to trigger a chemical reaction in skin. Before this can happen, a special cream containing a drug is applied to the diseased part of the patient’s skin making this area more sensitive to light. Performing the therapy in a hospital is reasonably straightforward but the underlying mechanisms of the chemical reaction are complex. A wide-range of specialists have been involved in researching and delivering

this therapy, which involves physics, biology, chemistry and medicine. We bring these specialisms together in this book, to explain in understandable language how the treatment works, breaking down the science that underpins this fascinating therapy.

Who are we?

We are a group of doctors and scientists, spread across a wide range of institutes in the east of Scotland.

- *Doctors, medical physicists, clinical technologists, biochemists and nurses from NHS Tayside;*
- *Doctors, engineers and physicists from the University of Dundee;*
- *Astronomers and physicists from the University of St Andrews.*

We have all come together at various stages to work with the Scottish Photodynamic Therapy Centre (SPDTC). The centre was established in 2001 and is supported financially by the Alfred Stewart Trust, a charitable organisation which was established by property developer Alfred Stewart in his Will to fund or support medical research and other charitable activities. The goal of the SPDTC is to promote the use, research and development of PDT. This “wee” book is made possible by funding from a Science and Technology Facilities Council Impact Accelerator Award. ■

Chapter 2:

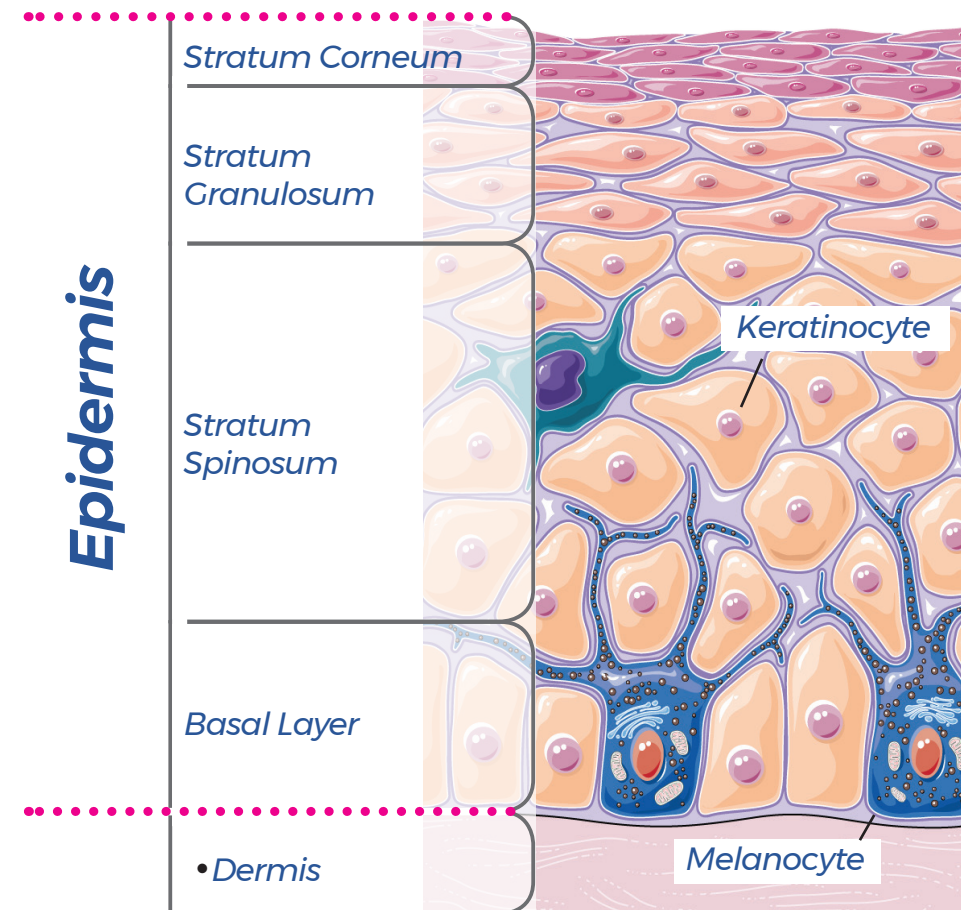
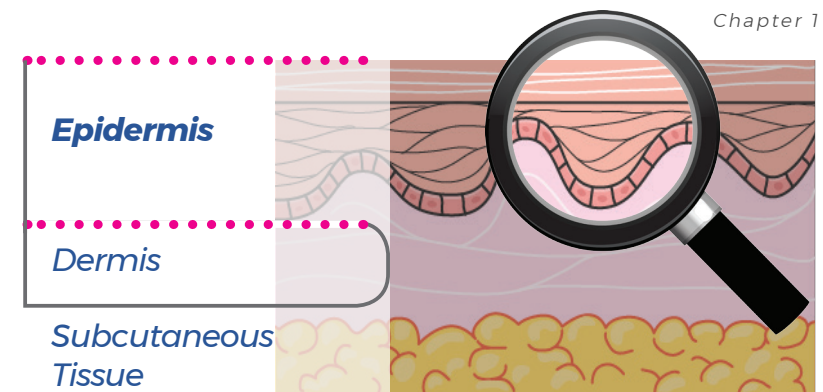
The skin

Definition: **Epidermis**

Of Greek origin, outer most layer of the skin. “epi” meaning over and “dermis” meaning skin.

Skin Cells

Skin is the body's largest organ and is made up of several layers (Figure 1). In the Basal layer, at the bottom of the Epidermis, two types of skin cells are made, Keratinocytes and Melanocytes. Keratinocytes form most of our skin cells and one of their main purposes is to create an environmental barrier, protecting us against a variety of dangers such as infections, heat, dehydration and radiation from the sun. In the early stages of their life cycle, keratinocytes are often referred to as Basal cells however as they mature, migrate and change shape they become Squamous cells. Melanocytes are responsible for producing melanin, which gives us our skin colour.



► **Figure 1.** Layers of the skin. “Adapted from: <https://smart.servier.com/category/medical-specialties/dermatology/>”

Life of a Keratinocyte

Keratinocytes are pushed up through the skin layers as the next generation of **Keratinocytes** form below



We can see and touch the dead cells in the **Stratum Corneum**. The cells are physically harder and will eventually fall from the skin surface.



In the **Stratum Granulosum** cells form a watertight barrier that helps prevent dehydration in the lower **Spinous** layer. Cells above this layer receive no nutrients.



Squashed as they travel through the **Stratum Spinosum**. This stops them from splitting and the cells can no longer replicate.



Produced by stem cells in the **Basal** layer. At this stage **Keratinocytes** are able to replicate.

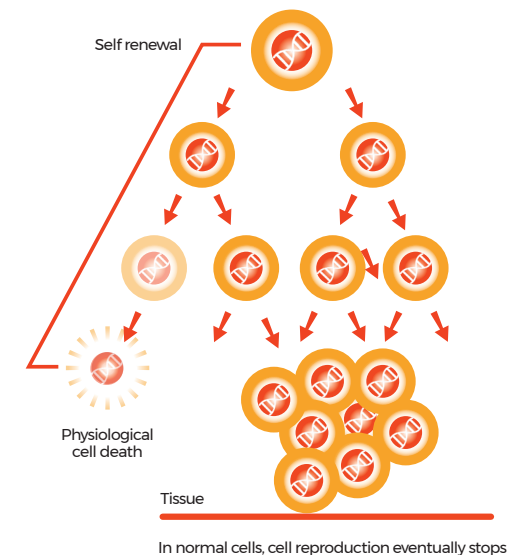
► **Figure 2.** Life Cycle of a Keratinocyte. "Adapted from: <https://smart.servier.com/category/medical-specialties/dermatology/>"

Damage to Skin cells

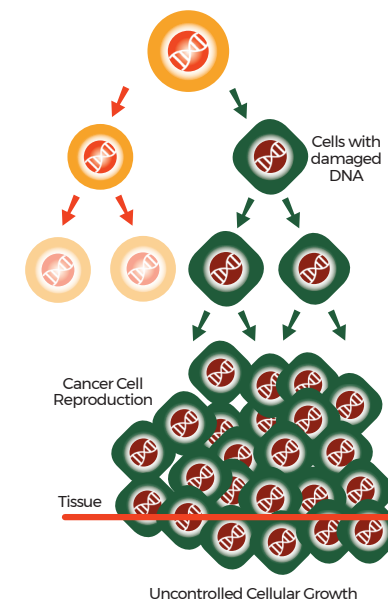
The first stage in the life cycle of a skin cell is growth, where the cell increases in size. Then it copies its DNA (deoxyribonucleic acid – carrier of our genetic code), prepares itself to divide before finally splitting, creating two identical cells. If the DNA in your cell is damaged, one of three things can happen:

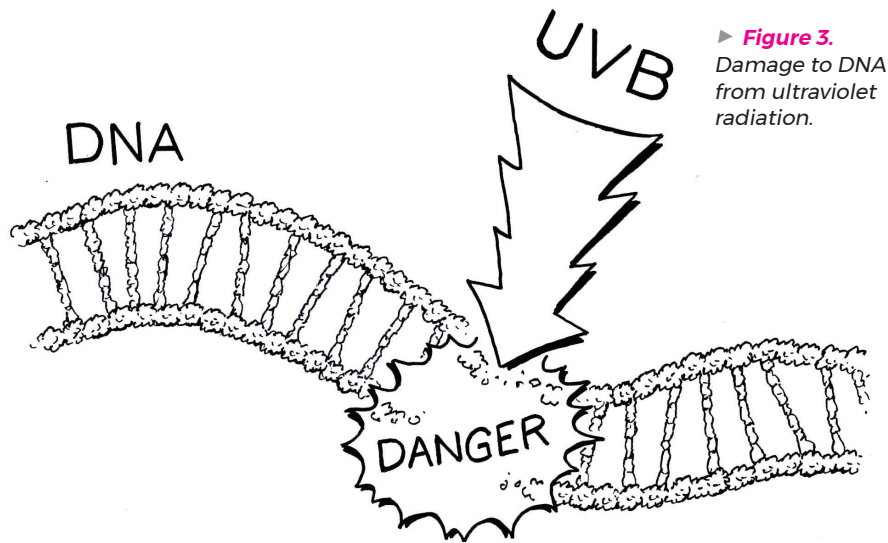
1. **It can repair itself and continue its life cycle.**
2. **It can determine that the damage is too severe and destroy itself.**
3. **It can mutate, copying the damage and continuing its life cycle with altered DNA, which will be passed on when the cell divides.**

A Healthy Cell Reproduction



B Cancer Cell Reproduction





► **Figure 3.** Damage to DNA from ultraviolet radiation.

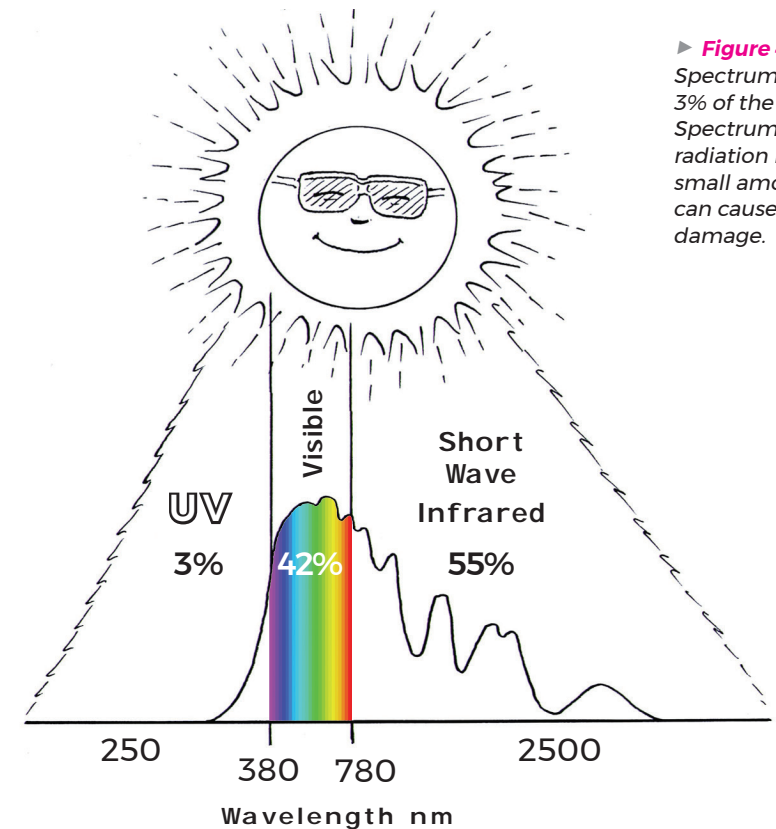
Ultraviolet (UV) radiation from the sun can penetrate through the skin and reach the Basal layer, damaging the skin cells.

Although your skin protects you from a lot of environmental dangers it is still possible for cells in the Basal layer to be harmed (Figure 3). If a keratinocyte becomes damaged in the Basal layer there is a small chance that it might become mutated and then split to produce more mutated cells and an accumulation of the DNA damage. The longer these cells remain in the Basal layer, the more they split, and the more modified keratinocytes can form. Over a period of years, the likelihood of these mutations taking place increases and eventually if there are lots of mutated cells, affected areas of the skin can be identified as being pre-cancerous or cancerous.

Ultraviolet radiation

Our main natural source of UV radiation is the sun (Figure 4). Although we often think of the sun as being yellow, it emits a broad range of radiation known as electromagnetic radiation. This includes every visible

colour as well as radiation that we cannot see, including UV radiation. Scientists have split UV radiation into three categories (UVA, UVB and UVC) corresponding to different energy ranges.



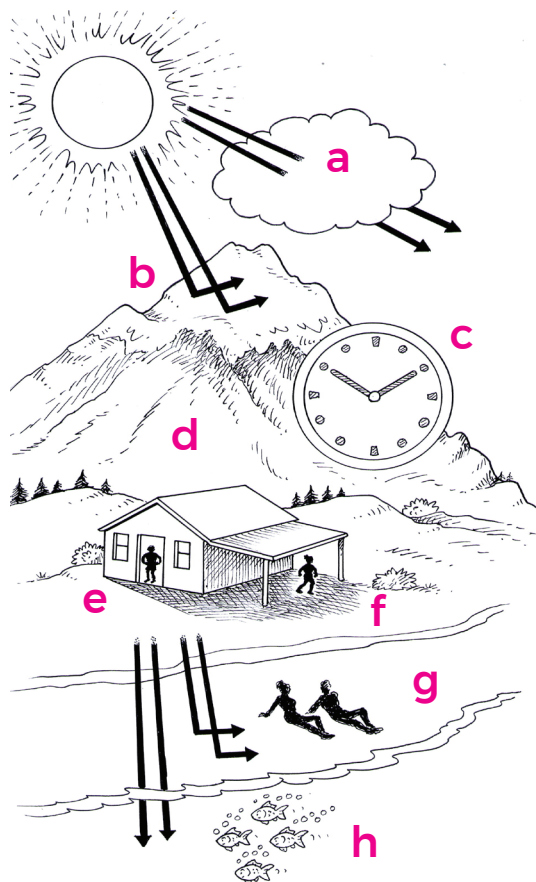
► **Figure 4.** Solar Spectrum. Only 3% of the Solar Spectrum is UV radiation but this small amount can cause a lot of damage.

UVC has the highest energy but due to absorption in the atmosphere it does not reach the Earth's surface. Both UVB and UVA however have a direct effect on us, penetrating our skin and reaching the Basal layer. UVA accounts for almost all (95%) of the UV radiation from the sun that reaches Earth and UVA penetrates deeper into the skin than UVB. However, UVB is much more (between 1,000 and 10,000 times more) effective at causing sunburn and, due to its higher energy, is also more likely to directly damage skin cells and DNA - although UVA still causes significant damage.

The amount of UV radiation reaching your skin depends on a number of things:

► **Figure 5.**

- 1. Location: UV radiation levels increase closer to the equator and at higher altitudes.**
- 2. Seasons: in general UV levels are higher in the summer than the winter, with UVB demonstrating larger seasonal variation than UVA.**
- 3. The surrounding environment and time of day is also important** (Figure 5). ■



- a.** Over 90% of UV can penetrate light cloud.
- b.** Clean snow reflects up to 80% of sunburning UV.
- c.** 60% of UV is received between 10am and 2pm daily.
- d.** UV levels increase by 4% for each 300 metre increase in altitude.
- e.** Indoor workers receive 10% to 20% of outdoor workers yearly UV exposure.
- f.** Shade can reduce UV levels by 50% or more.
- g.** White sand reflects up to 15% of UV.
- h.** At half a metre depth UV is still 40% as intense as at the surface.

Chapter **3**:

Sun-damaged skin

If you are concerned about a mark that you have that has changed or has just appeared on your skin, particularly if it has changed size, shape or colour, or has started to cause you discomfort, then seek advice from your doctor urgently. The doctor will examine the skin, looking at characteristics such as size, shape, colour and texture of any mark. They may also remove a small sample of skin (known as a biopsy) and send it to a laboratory to be examined under a microscope.

In this chapter we will summarise some of the pre-cancerous and cancerous skin diseases, which can result from solar UV radiation causing DNA damage and mutations in keratinocytes. These are known as non-melanoma skin cancer (NMSC). Melanoma, the most aggressive form of skin cancer, is the result of mutations in melanocytes and will not be covered here as melanoma is not treated by PDT.

Actinic Keratosis (AK)

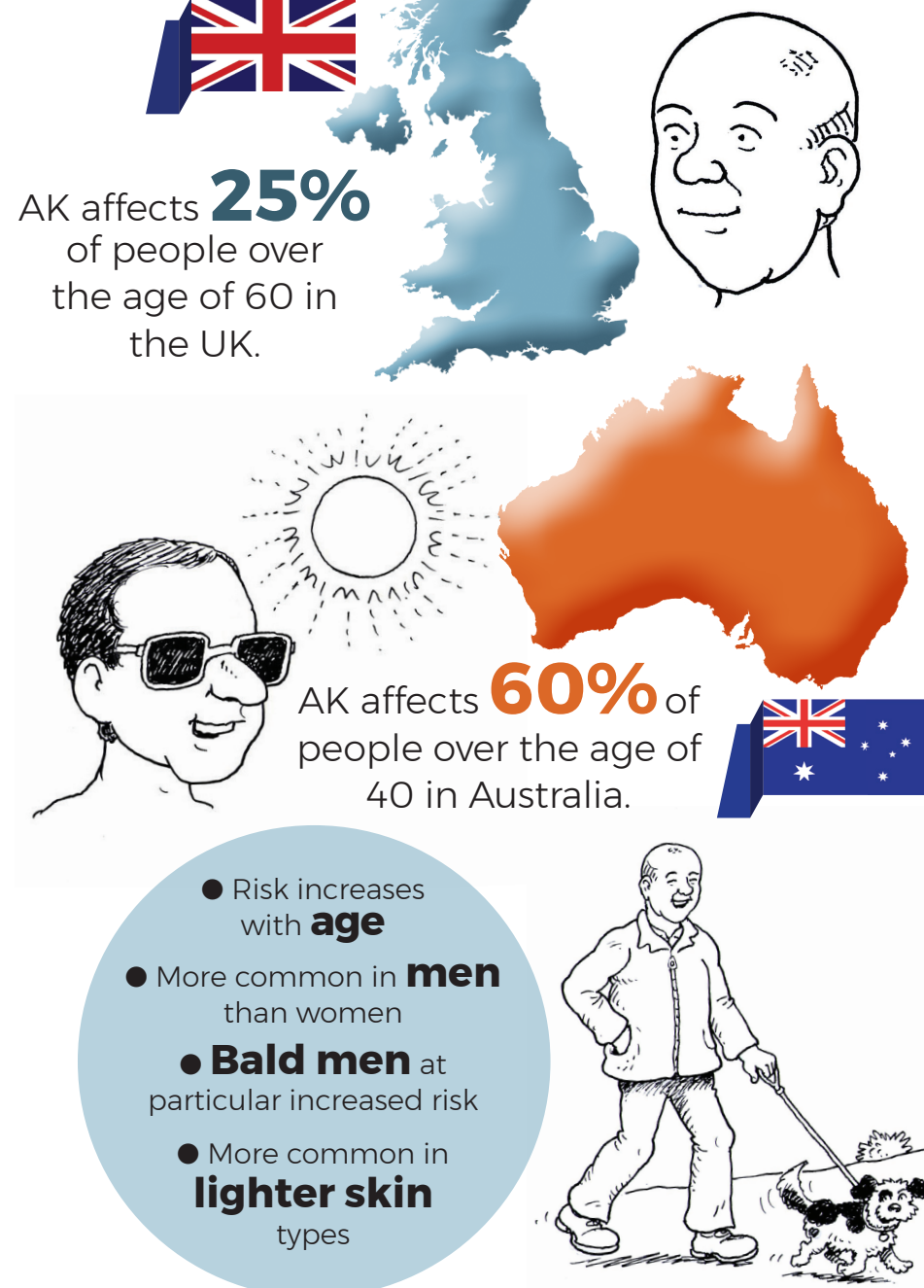
Definition: **Actinic keratosis (plural keratoses)**

Known as **AK**, comes from the Greek "actinic" due to the sun and "keratosis" a thickening of the skin.



► **Figure 6.** Large area coverage of AK on the scalp of a bald man, which is a typically sun exposed part of the body.

► **Figure 7.** Facts about AK



Generally AK are fairly harmless and are characterised into 3 grades:

- 1. Grade I mild AK. Tend to be felt rather than seen but can resemble a honeycomb pattern on the skin. They feel rough with a sandpaper like texture.**
- 2. Grade II moderate AK. These are red and scaly lesions that can look like warts.**
- 3. Grade III severe AK. These cause severe thickening of the skin. They are raised hard warty lesions that tend to have a noticeable honeycomb pattern and feel hard and craggy to the touch.**



► **Figure 8.** There is a small risk that AK can transform into more dangerous squamous cell carcinoma (SCC), which can be invasive and spread to other parts of the body (metastatic) if it isn't treated.

It is thought that people with numerous areas of AK have a 10% chance of developing a skin cancer, called a squamous cell carcinoma (SCC) within 10 years of their AK appearing (*Figure 8*). This is why AK are usually actively treated even though, in their usual form, they are generally harmless.

AK usually occur as a result of years, or even decades, of exposure to ultraviolet radiation from the sun. The damage caused can't be fully reversed and so while it is possible to treat AKs they will often reappear after treatment or new ones will develop (sometimes they also just disappear without any treatment). A long-term approach to managing AKs is needed because overall the treatment costs to the healthcare service are high. An important part of managing AKs is raising awareness, so that sun exposure is limited in the early years of life which will reduce lifetime UV exposure and sun damage and hopefully limit the number of future AKs. Using sunbeds, working outdoors and even your genetic makeup (for example if you burn easily) can increase the risk, although AKs are not hereditary. Other contributing factors for AK formation are immunosuppression (this includes people who take immunosuppressive drugs e.g. organ transplant patients) as well as individuals with human papillomavirus (HPV).

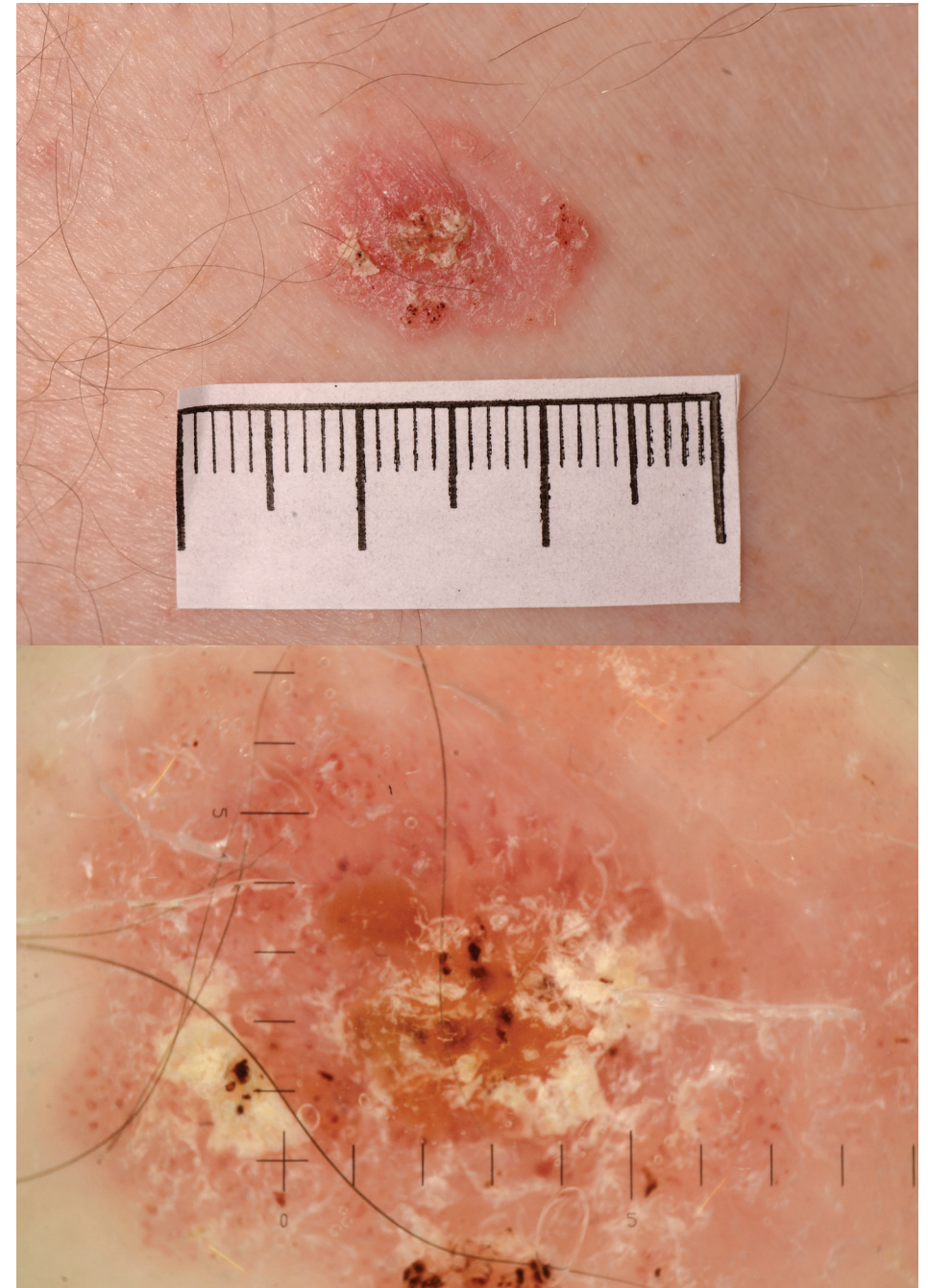
Bowen's Disease

Bowen's disease (also referred to as SCC in situ) is an early form of SCC – there are cancerous skin cells present but they are 'in situ', which means they are on the surface and haven't spread deeper into the skin. Bowen's disease usually presents as red, scaly patches on the skin and this can be confused with psoriasis or eczema. (*Figure 9*). If Bowen's disease is left untreated, there is a small chance that it can spread deeper into the skin becoming an invasive SCC. However, most Bowen's disease does not go on to this type of invasive skin cancer.

Bowen's disease typically forms on sun-exposed skin, although lesions can also occur on covered sites such as the genitals. The commonest site is the lower legs of elderly women. Bowen's disease does appear to be a consequence of long-term sun-exposure and like AK, it is more likely to occur in individuals that are immunosuppressed or have HPV. Bowen's disease is not hereditary.



► **Figure 9.** Bowen's disease lesion on the arm



► **Figure 9.** A close-up (top) and a dermoscope image (bottom) of the same lesion.

Squamous Cell Carcinoma (SCC)

Squamous Cell Carcinoma (SCC) is an invasive NMSC and like the diseases already mentioned, it is primarily caused by long term exposure to UV radiation from the sun (*Figure 10*). Although SCCs typically occur on sun-exposed areas of the skin, they can form anywhere on the body. As mentioned earlier, SCCs can also develop from pre-existing AK or Bowen's disease.



► **Figure 10.** SCC on the leg

Exposure to the sun, being male, genetic makeup particularly sun sensitivity skin type, immunosuppression such as in organ transplant patients, and people with genetic diseases that predispose them to skin cancers (e.g. albinism and xeroderma pigmentosum) are all factors which increase the risk of developing SCC. Fortunately, SCCs may be fairly slow growing and, when caught early, are usually easily treated. They normally appear as a crusty/scaly growth where the skin forms a red, raised,

firm lump. The area can be painful and tender, the surface can break down and can sometimes bleed if bumped or scraped. Appearances can also vary, and SCC can turn to an ulcer. If left untreated, SCC will spread into different tissues in the body through the lymph glands or blood, forming secondary deposits of cancer (metastasis).

Basal Cell Carcinoma (BCC)

Basal Cell Carcinoma (BCC) is the commonest cancer in Caucasians and is by far the commonest form of skin cancer. It originates from cells in the epidermis although the exact cells involved are not as clearly understood as for SCC. Long-term UV exposure is a major risk factor for BCC which typically occurs on sun-exposed areas. Other risk factors are the same as for AK, Bowen's Disease and SCC. Immunosuppression and HPV are not thought to be risk factors for BCC. Whilst they are not usually hereditary there are rare genetic conditions such as Nevoid BCC syndrome (Gorlin-Goltz syndrome) and xeroderma pigmentosum (XP) which drastically increase the risk of BCC.

BCCs vary in appearance and can be nodular (lumpy) or a scaly flatter red mark (*Figure 11*). They can appear as a scab that continually bleeds



► **Figure 11.** Nodular BCC on the nose (left) and superficial BCC on the lower back (right).

but does not heal and, if left untreated, an ulcer can form. BCCs are usually diagnosed by their appearance as they often have a raised rolled pearly edge, seen best when the skin is stretched. Skin biopsies may be performed. BCCs characteristically do not spread to other body parts, although they can destroy important cellular structures through invasive growth locally if they are left untreated. They can usually be treated easily although it becomes more complicated when they occur at risky body sites (such as the eyes, ears and nose) or when they are left untreated for a long time. BCC is only very rarely fatal; this happens if left untreated. It is very likely that if someone develops a BCC or SCC, they will go on to develop more in their lifetime. ■

- *Skin cancer accounts for about 1/3 of all cancers*
- *9 out of every 10 skin cancers are non-melanoma skin cancers (NMSC)*
- *BCC is the most common type of skin cancer*
- *SCC is the 2nd most common type of skin cancer*
- *BCC are often called “rodent ulcers” because they gradually destroy the skin going deeper into its structure, like a rodent, and if left untreated can cause an ulcer*

Chapter 4:

Treatment for sun damaged skin & NMSC

It is essential to overview all the treatment options available and it is important to have choice as what might suit one person may not be ideal for another.

Treatment for skin cancers and pre-cancers mentioned previously fall into two categories:

- 1. Lesion directed – treatment of a single small area of diseased skin. Examples include surgery and cryotherapy.**
- 2. Field directed (can also be used as lesion directed treatments) – treatment of a larger field of skin that includes several areas of skin pre-cancer and/or cancer within it. Examples include applying drugs in the form of creams to the skin and, the focus of this book, PDT.**



► **Figure 12.** Scar on the left shoulder resulting from surgery. A BCC is visible beside the scar

Lesion directed treatments

Surgery

- Effective lesion directed treatment for removing NMSC.
- Crucial for invasive NMSC such as SCC and typically used for thicker types of BCC.
- Performed under local anaesthetic (numbing the area so that pain is not felt).
- The affected area of skin is removed along with a rim of surrounding healthy skin to make sure no cancer cells are left behind.
- Afterwards the skin is usually stitched up or occasionally a skin graft may be needed (*Figure 12*).

Cryotherapy

- Uses the extreme cold of liquid nitrogen (between -25°C to -50°C) to freeze the skin area - as thawing occurs this causes damage and eventual death of the affected pre-cancerous or cancerous cells. Immediately after cryotherapy the skin becomes red, swollen and can sometimes blister.
- Scarring can sometimes occur with cryotherapy.
- Lesion directed treatments are often not the best approach for pre-cancerous change and for the more superficial NMSC. This may be because the affected area that needs to be treated is too large or there are too many lesions or because there may be problems with skin healing at certain body sites. Often there are also areas within a “field” that are not easily visible and these will be missed with lesion directed treatment but not with field directed treatment. Also, as most pre-cancerous changes and NMSC occur on locations of the body which are exposed to the sun, visible scars can be undesirable.

Field directed treatments

5-Fluorouracil (5-FU)

- Most effective choice for multiple AK with highest clearance rates and longest time without recurrence.
- Targets the fast-growing abnormal pre-cancerous or cancerous cells in areas of the skin where it is applied and destroys them leaving the healthy areas undamaged.
- Typically applied in a cream once or twice daily for 3-4 weeks.
- Causes inflammation (the body’s response to injury, which appears as redness and swelling in the skin), crusting and discomfort during

treatment, which may last for several weeks and can be difficult for patients to tolerate.

- If not applied properly or regularly then there may be a less effective outcome, so it is dependent on the patient or their carer being able to treat themselves.

Imiquimod

- Triggers an immune response at the treated site, adapting the skin's immune system to recognise and react against diseased tissue resulting in inflammation and destruction of abnormal cells.
- Typically applied to the affected area as a thin lotion 3 days a week, at night, allowing it to absorb into the skin for 8 hours before being washed off the following day. This treatment regime continues for 4 weeks for AK. If used for superficial BCC then it will be applied 5 times a week for 6 weeks..

Diclofenac gel

- Nonsteroidal anti-inflammatory gel that is only used to treat AK.
- It is applied as a gel to the sun-damaged area, twice daily, for 60 to 90 days.
- As with the other topical drugs, there may be side effects with this treatment, which include inflammation and discomfort, although these are usually minor.

Other

- Radiotherapy may occasionally be used to treat invasive NMSC such as SCC, particularly when surgical options are not possible. The tumour is exposed to ionising radiation in a controlled procedure and is done over the course of numerous treatments.

- Very uncommonly NMSC, particularly invasive SCC, can metastasise to other parts of the body and then chemotherapy may be needed - as is the case for other types of metastatic cancer.

Photodynamic Therapy (PDT)

PDT is an effective treatment for either single lesions or for large treatment areas of pre-cancerous sun damage changes (AK and Bowen's disease) and/or certain types of NMSC, particularly superficial BCC. It is different from all the other treatments mentioned thus far as it uses not just a drug, but also light and oxygen to kill the diseased cells (Figure 13). ■



► **Figure 13.** PDT being performed on a lower leg.

Chapter 5:

Photodynamic therapy

Definition: **Photo**

Of Greek origin, means “light” when it is combined with another term to form a word. For example, photography which is a light (photo) drawing (graphy).

Background

In 1900, medical student Oscar Raab discovered during a thunderstorm that certain drugs would interact with light and kill cells. Oscar Raab’s mentor Professor Hermann von Tappeiner (a skin specialist who came up with the term photodynamic therapy PDT) started experimenting with these drugs on the skin and, with a white light, successfully treated some skin cancers. He showed that when used on their own both the drug and the light were harmless. However, when added together, and in the company of oxygen, damaged cells could be destroyed (Figure 14).

PDT for precancerous skin changes and non-invasive NMSC is a straightforward treatment to perform and receive - a cream containing the drug is applied to the skin in the area to be treated, there is a period of waiting and then a light is shone on the area.

Drug

For PDT of the skin, a cream containing a

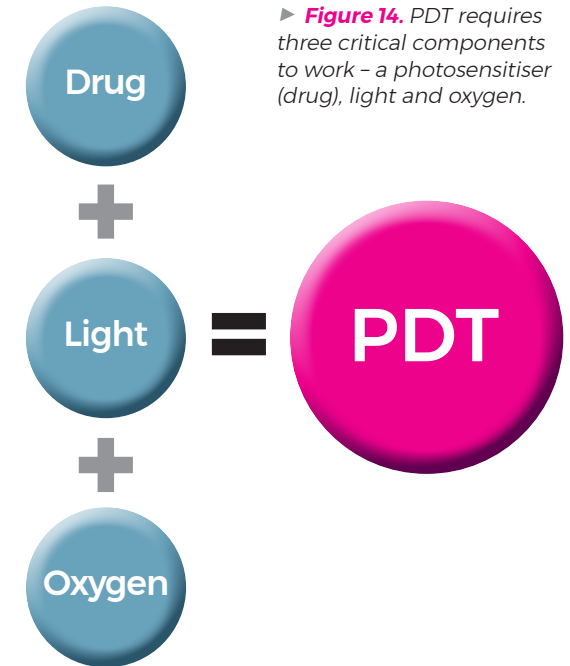
prodrug is used. There are

two common types of **prodrug**:

1. 5-aminolaevulinic acid (5-ALA)

2. methyl aminolevulinate (MAL)

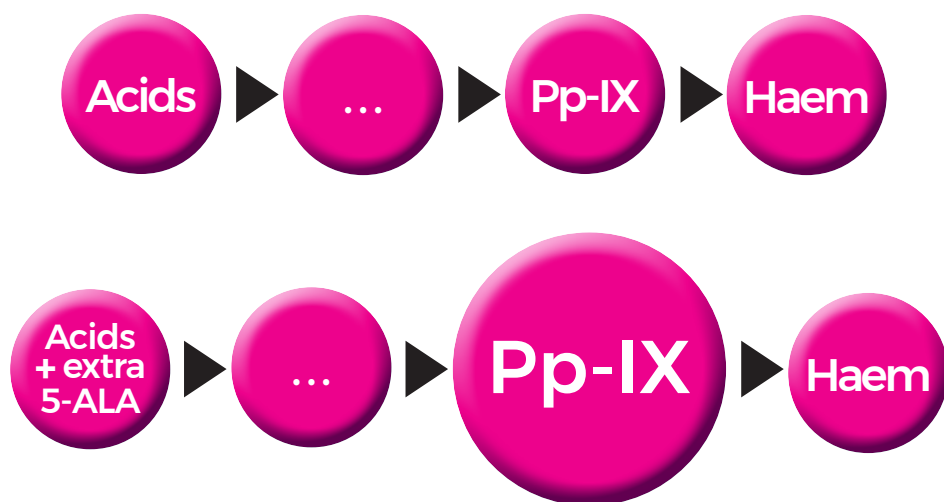
The prodrug (cream) is absorbed by the skin and changed by the skin cells into a chemical that is sensitive to light, known as a photosensitiser. The uptake and conversion processes happen more quickly in cancerous cells, resulting in more photosensitiser in the tumour than in the surrounding normal skin. The photosensitiser remains in the skin cell until it is either activated by light or is changed further by the cell (see next section). The photosensitiser cannot be transferred to other cells which means the light sensitive area is restricted to where the cream has been applied. Typically, the prodrug (cream) will be left on the skin to absorb for between 30 minutes to 3 hours.



► **Figure 14.** PDT requires three critical components to work – a photosensitiser (drug), light and oxygen.

How is the prodrug changed into a photosensitiser?

The conversion process in the skin cells, which changes the prodrug into a photosensitiser, is known as the “haem cycle” and is the main process in haemoglobin metabolism. It is a natural process in a cell that takes certain acids and converts them into light sensitive chemicals called porphyrins. Iron from the body is then added to change the porphyrins into haem – the red substance in blood that transports oxygen. When extra acids (e.g. 5-aminolaevulinic acid) are introduced to the skin cells from the prodrug they are converted into porphyrins by the same natural process described above. However, the next stage in the metabolism, adding iron, is a slow process and it can't cope with these extra porphyrins so they build up in the skin. In particular there is a build-up of one porphyrin - protoporphyrin nine (known as PpIX).



Light

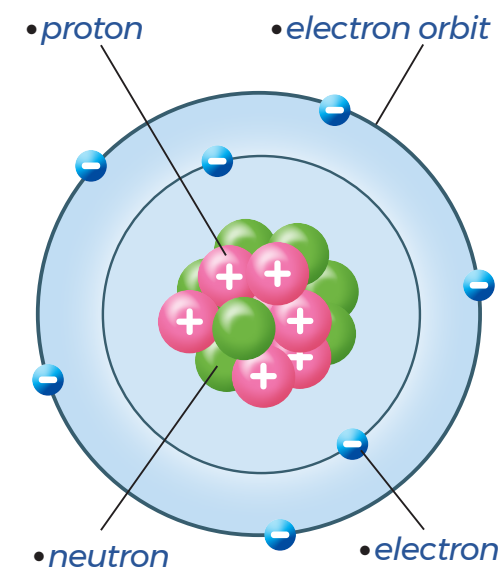
When light shines on skin that is full of light sensitive PpIX, the light energy is absorbed. This makes the PpIX excited, which it doesn't like, and it wants to get rid of the extra energy it now has. But what does the excitation process look like and how does it get rid of the energy?

History

In 1911, Ernest Rutherford proposed a theory for the structure of an atom. In 1913 Niels Bohr proposed his model, that built on Rutherford's, describing the structure of a hydrogen atom (Figure 15). Here, Bohr depicted a solar system type arrangement where there was a tight positive core (i.e. the Sun) and electrons orbiting around it (i.e. planets). Later advancements in quantum mechanics showed fundamental errors in this theory however the Bohr model is an effective method to describe how electrons travel through different energy levels that occur within atoms.

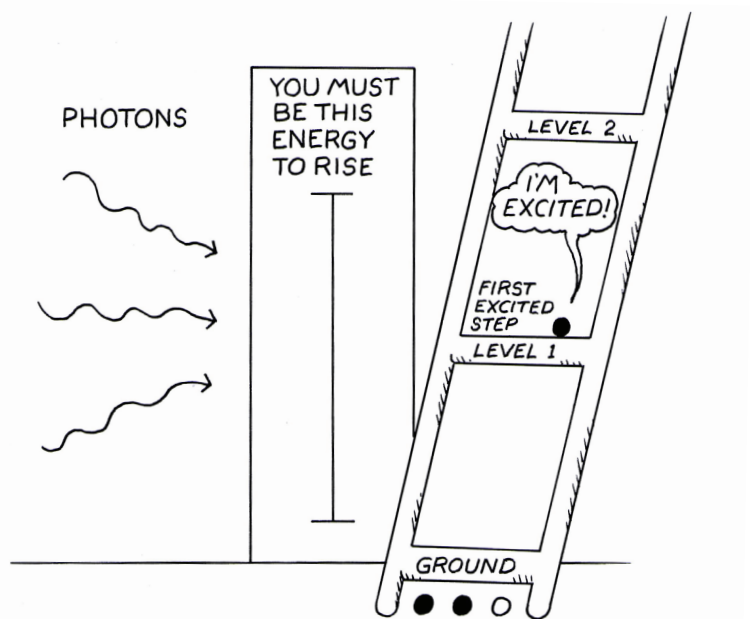
Energy Levels

Energy levels in an atom appear like rungs on a ladder, with the ground being the lowest energy level, known as the ground state. Each step up on the ladder requires more energy than the previous step. The photosensitiser PpIX has electrons on the ground level and external energy must be



► **Figure 15.** An example of Bohr atomic model

absorbed to move an electron out of the ground level. In PDT, this is achieved by using light of a specific energy (at least the same as the energy of our first level) to excite the electron onto a higher energy level (Figure 16).



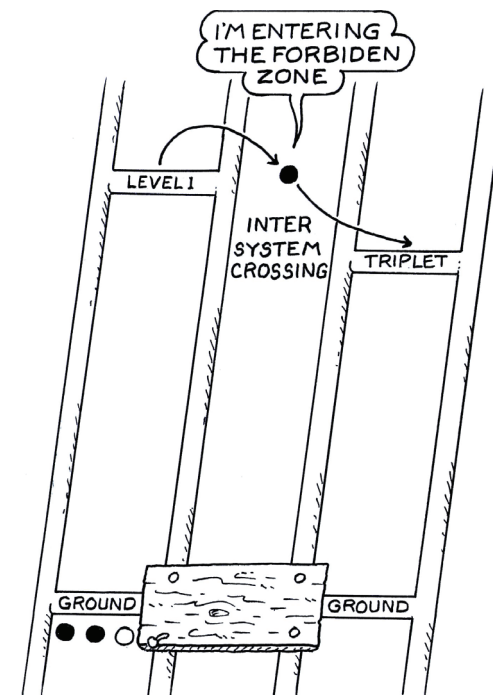
► **Figure 16.** Incoming light provides energy that moves an electron from its ground state to the first excited level.

When the photosensitiser absorbs the light energy, it moves onto the first excited level leaving behind a hole in the ground level. However the first excited level is not the only excited level in which an electron can exist - there are additional higher energy levels further up the ladder. There is also a forbidden transition, known as the triplet state (Figure 17). The triplet state can be thought of as another energy ladder that shares the ground level with the first energy ladder.

Excited electrons don't like having extra energy, they want to lose it and return to the ground level which they can do in two different ways. The first is called non-radiative, energy is lost by emitting heat

or vibrating. The second is called radiative, where energy is lost by emission of light. The light that is emitted has less energy than the light that was originally absorbed. The process that allows electrons to switch from the 1st excited level to the lower energy forbidden triplet state, is known as intersystem crossing and is non-radiative.

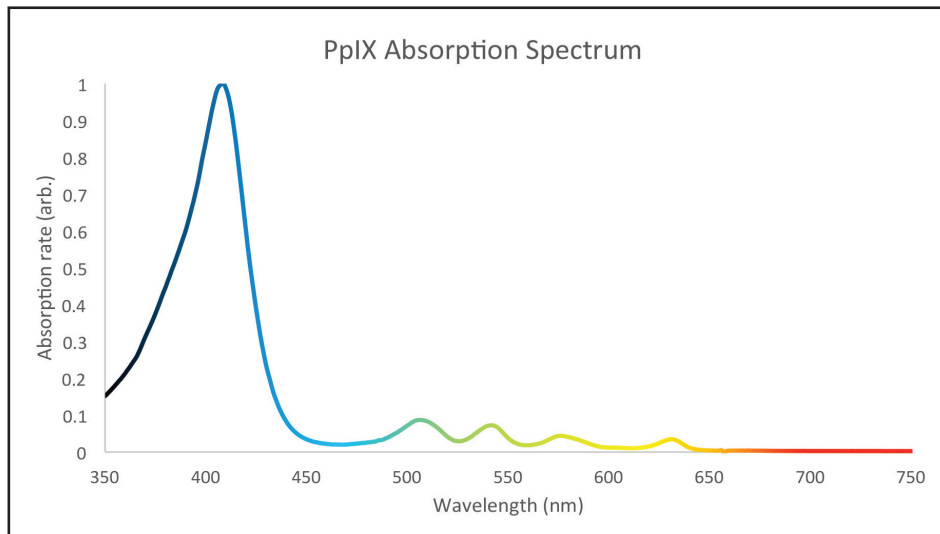
For PDT we want the excited PpIX electrons to be in the forbidden triplet state because this allows time for the energy to be transferred to the third and final component required for PDT - oxygen.



► **Figure 17.** The triplet state and intersystem crossing.

Protoporphyrin-IX

PpIX prefers to absorb blue light (Figure 18) but it can also absorb other energies of light too (light with different energies appear to our eyes as different colours). Red light is used for most PDT for NMSC, it isn't as efficient as blue light but travels deeper in the skin to reach damaged cells. Blue light or white light can also be used to treat AK, as these damaged cells are located in only the most superficial parts of the skin.



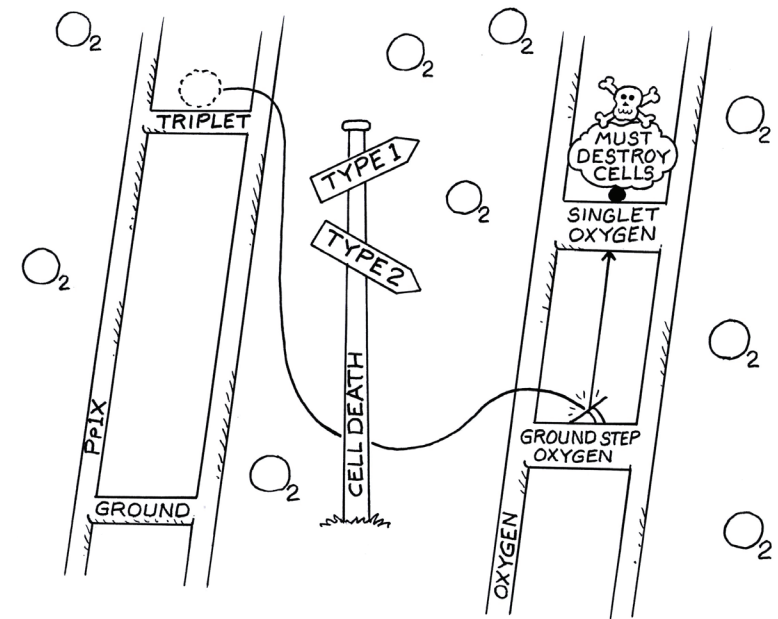
► **Figure 18.** Protoporphyrin-IX absorption curve.

Oxygen

Oxygen is vital for our cells. Once we breathe in oxygen it enters our lungs and is transferred to our blood. It is then sent to the heart which pumps the oxygenated blood around our bodies. The cells of our bodies (including our skin cells) are supplied with oxygen from this blood but skin is also supplied with oxygen from the atmosphere, creating a large available quantity.

As described already, intersystem crossing allows some of the PpIX's electrons to be in an excited triplet state when light is being shone on the treatment area. Excited PpIX wants to transfer its energy to something else, where the 'something else' in this case is oxygen. It does this in two ways, called a type 1 or type 2 reaction. Both cause stress and damage to our cells but type 2 is the preferred reaction for PDT. As the PpIX transfers its energy to oxygen, there is enough energy from the PpIX to excite the oxygen into its first excited state, in oxygen's own ladder. This creates singlet oxygen which is

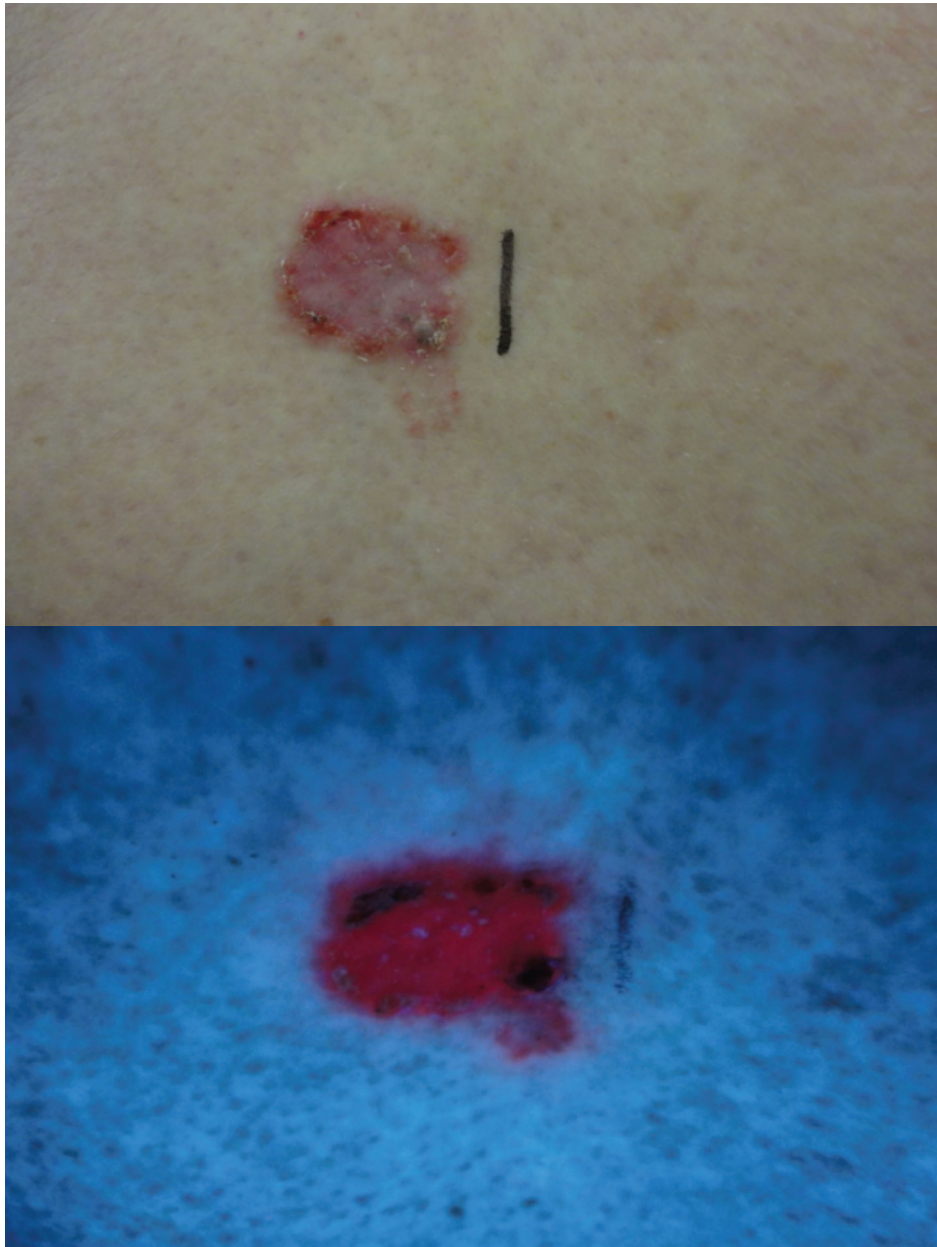
extremely toxic to living cells. As the singlet oxygen, which is in an unstable excited state, transfers back to its ground state it releases its energy causing cell death and destroying the diseased tissues (Figure 19). The photodynamic therapy process is complete!



► **Figure 19.** Exciting oxygen.

Fluorescence

When violet light is shone onto a photosensitised lesion, the lesion emits red light (glows red), which is known as fluorescence (Figure 20). Fluorescence is an example of radiative energy loss - the light being emitted (red) has lower energy than the light used to excite the photosensitiser (violet) ■



► **Figure 20.** BCC under normal lighting conditions (top) and illuminated by violet light (bottom). The violet light is absorbed by the PpIX in the BCC and electrons are moved into the first excited level. This isn't stable and they get rid of their energy by releasing red light (fluorescence).

Chapter 6:

PDT for pre-cancerous skin changes & superficial non-invasive NMSC

Broadly speaking there are two different PDT techniques commonly used to treat pre-cancerous skin changes and superficial NMSC. These are known as Conventional PDT and Daylight PDT.

Conventional PDT

Conventional PDT is currently used to treat:

- **Actinic Keratosis (AK)**
- **Bowen's Disease (BD)**
- **Superficial Basal Cell Carcinoma (BCC)**

For AK a single treatment is performed and for Bowen's disease and BCC a second treatment is performed one week after the first treatment. The area is reviewed at 3 months by a healthcare professional and the process repeated if diseased skin remains.



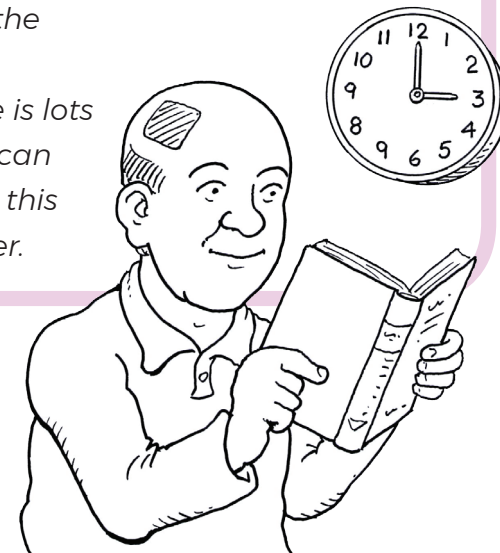
1. Once a patient arrives at their treatment centre the area of skin that is going to be treated will need to be assessed and prepared

2. Crusts and scales on the skin are removed by gentle scraping, usually with a disposable instrument that looks like a mini ice cream scoop (this is called curettage). This doesn't need any local anaesthetic as the procedure is not too uncomfortable. The scraping roughens the skin and allows better absorption of the prodrug.

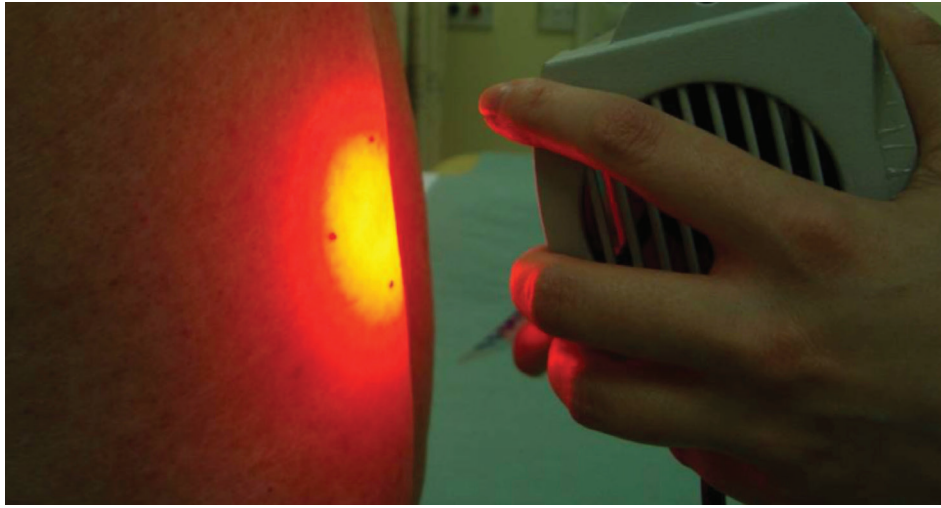


3. The prodrug is applied to the affected area, normally with a spatula or gloved finger. A small border of normal skin surrounding the treatment area also has the prodrug applied to make sure all of the disease is being treated.

4. Once the cream application is complete the areas are then completely covered with dressings so that no light reaches them. This is referred to as occlusion. During occlusion the prodrug is being taken up and converted by the damaged cells into the photosensitiser PpIX, and is accumulating so that there is lots of it available. The patient can normally leave the clinic at this point, returning 3 hours later.



Upon returning to the treatment centre, the dressings are removed, and the prodrug wiped off. A lamp is positioned over the treatment area, which is then illuminated with a bright red light (Figure 21). As previously described the light energy is transferred to the photosensitiser, which in turn passes the energy to oxygen and the resulting energy release in oxygen destroys the damaged cells. The light will stay on until enough of the light's energy has been absorbed by the photosensitiser. Typically this takes between 5 and 20 minutes. Treatment is finished once the light is switched off.



► **Figure 21.** PDT being performed on the back.

The light

The most common light used for PDT in skin is red LEDs (light emitting diodes). Red is chosen because of its ability to penetrate further into the skin than higher energy colours such as green or blue. Red LEDs are very efficient and can produce a lot of energy over a reasonably large area, allowing them to treat multiple nearby locations at once. Laser light can also be used as can filtered white light, but these are far less common.

Daylight PDT

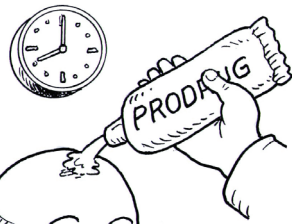
Daylight PDT is like conventional PDT but with a few key differences. First is that daylight PDT is only used to treat AK. It is somewhat ironic that the AK are caused by the sun (the ultraviolet radiation part) and can also be treated by the sun (although this time it's the visible light).



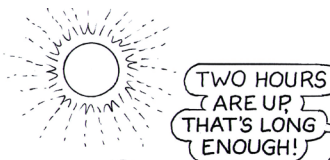
1. Upon arriving at the treatment centre, a nurse or healthcare professional will assess the area requiring treatment and then apply a sunscreen to all the patient's sun exposed sites. Sunscreen is specifically chosen so that it does not interfere with treatment but does block the sun's UV radiation. Careful sunscreen choice is essential as some sunscreens will block some of the visible light that is required for PDT and can reduce the amount of light the patient receives during treatment.



2. After 10 minutes crusting and flaky skin is removed from the AK (using same methods as for conventional PDT)

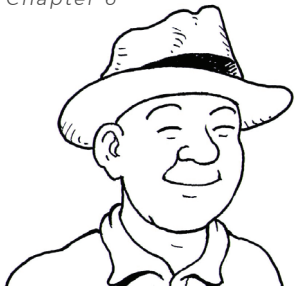


3. The prodrug is applied but the treatment area is not occluded.



4. Within 30 minutes the patient goes outside and exposes the treatment area to direct, natural daylight for at least 2 hours. What they do during that time is up to them. Some garden while others walk the dog or sit (outside) at a café.

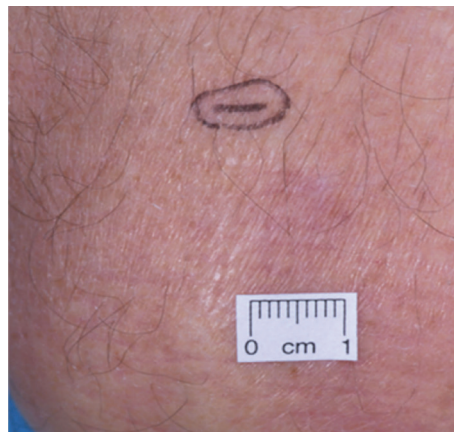
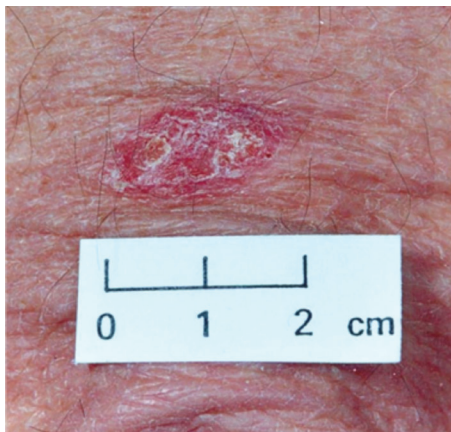




5. After 2 hours the patients wash the area that the prodrug was applied to and either cover it up with clothing or stays indoors.

Benefits of PDT

- **Effective evidence-based treatment for licenced indications (AK, Bowen's Disease, BCC).**
- **Good cosmetic outcome, with minimal or no scarring (Figure 22).**
- **Skin feels 'fresher'.**
- **High levels of patient satisfaction.**
- **Good patient compliance, no need to apply creams regularly for several weeks.**
- **Very low levels of discomfort with Daylight PDT.**



► **Figure 22.** Before (left) and after (right) hospital-based PDT shows an excellent cosmetic outcome.

Side Effects

As with all treatments, there are some known side effects which can occur with PDT, although some are less of a side effect and more of a positive treatment response as they indicate that the desired reaction has taken place.

- **Inflamed skin - red, swollen and tender (Figure 23).**

This is the consequence of the photodynamic reaction and shows that treatment has occurred.

Happens frequently, starts immediately after treatment and usually clears within a few days, although can occasionally last longer.

- **Pain during treatment (Conventional PDT)**

The photodynamic reaction causes pain.

Higher pain levels experienced when:

- treating large areas
- treating the face or scalp and AK
- using intense light sources

Particularly problematic when treating AKs on the face or scalp with conventional PDT, which is why nearly painless daylight PDT has effectively replaced conventional PDT for AK.

As the factors that are associated with pain are now well known, it is very rarely a treatment-limiting problem with PDT.

- **Allergic skin reaction**

Rare, estimated at approximately 1 - 2% of patients

Higher risk if large areas being treated several times



► **Figure 23.** Red, swollen and tender skin immediately after PDT.

Other Factors

It is really important to assess the specific needs of each patient individually. One size does not fit all! PDT is often preferred to surgery because it doesn't leave a scar and surgery would not be possible for large areas of sun damage. PDT may also be preferred to 5-FU and Imiquimod because there isn't a requirement to apply treatment at home regularly for several weeks.

However, there are factors to consider before providing or receiving PDT.

Conventional PDT takes time to deliver and is repeated a week later for non-invasive NMSC, with potential for further treatment in three months if not clear. Daylight PDT is more time efficient and

can be performed in the home setting, but is only appropriate for AK. There is a 2-hour exposure to daylight required but many who undergo this therapy enjoy the outdoor treatment period.

The obvious potential downside to 'daylight' PDT is that it needs reasonable weather conditions. It can't be raining and it can't be too cold, which usually limits treatment in the UK to months between April and October. Planning an appropriate treatment day can be challenging, but a bright day will always have enough light for treatment within a 2-hour period and if we can do it successfully in Scotland then it should be manageable in most other locations.

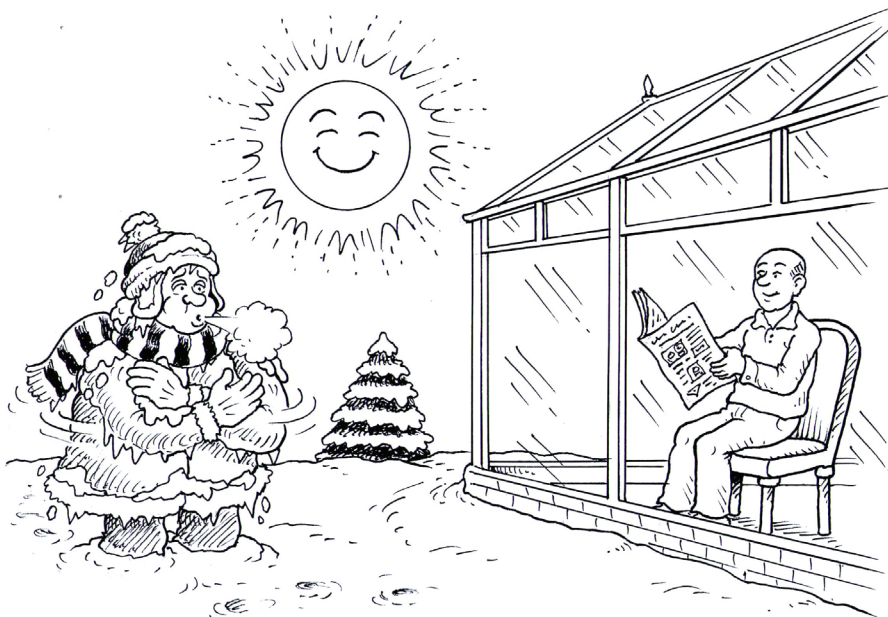
Various research groups are trying to find ways to be more accurate with the light exposure by using wearable light detectors or satellite images. In the future this might help reduce the length of the treatment but at the time of writing the recommendation remains a standard 2 hours of daylight.

Expanding on daylight

Daylight PDT is typically administered between April and October in the UK. The reason for excluding winter months is not due to light levels being too low but the temperature. Daylight PDT is not usually administered when temperatures are under 10°C as this is, based on experience, deemed too cold to ensure compliance with treatment. The downsides to daylight PDT have led to imaginative solutions for overcoming the challenges, for example with temperature control such as conservatory-based PDT (Figure 24).

The glass in the conservatory filters out harmful UVB, allows in the visible light to perform the treatment but also allows temperature to remain constant and comfortable. This means when its bright but cold outside, treatment can still take place inside.

Another area of research is the creation of light sources that mimic the sun, allowing patients to remain indoors for their treatment. Wearable technology for PDT, fibres that are woven into sheets with red light passing through them, are also now available. Effectively the patient is wearing clothes that 'glow' red. These fibres are placed over the diseased areas, after prodrug application, and are left to illuminate the area for a time until a certain amount of light is delivered. ■



► **Figure 24.** Conservatory based PDT

Chapter **7:**

What else is PDT used for?

At the time of writing, the British Association of Dermatologists state that PDT should be considered for prevention of future NMSC in high risk patients, such as organ transplant recipients. It should also be considered for some pre-cancerous genital conditions, treatment resistant warts, as an option for acne and as an anti-microbial treatment. Whilst PDT has been investigated in a lot of other conditions there is, as yet, not enough evidence to support PDT for many of these diseases, including alopecia, hypertrophic scars, rosacea and wound healing. There is good evidence that current PDT approaches are not effective for psoriasis and should not be used for this purpose.

PDT is gaining popularity in the private sector as it is believed to have a rejuvenating effect on the areas of skin it is applied to, making the area look and feel younger, removing fine wrinkles, and being

marketed as an anti-aging treatment. However, there isn't enough evidence available yet to support recommending PDT for this purpose.

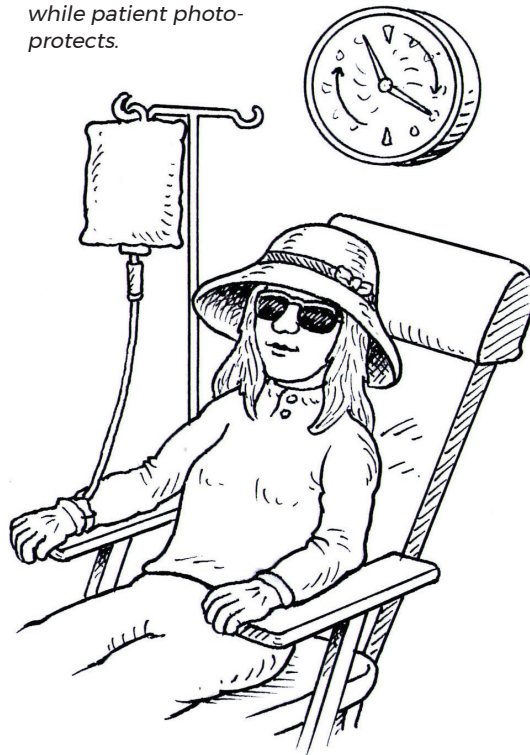
Whilst PDT is a routine treatment in dermatology, it is a less common therapeutic approach for cancer affecting other organs although there is a lot of research in using PDT to treat a wide range of cancers.

PDT for internal diseases

When considering PDT for diseases within the body (often called systemic PDT) the underlying processes (light, oxygen, photosensitiser) are the same as PDT for skin, however there are some important differences in the way the treatment is performed.

For PDT within the body a cream cannot be applied to the treatment area and therefore the photosensitiser is delivered as either a drink or an injection and there is no need for a pro-drug phase. The photosensitiser will circulate around the body and be preferably taken up in the cancerous cells. The photosensitiser is given time to build up within the cancer cells – the length

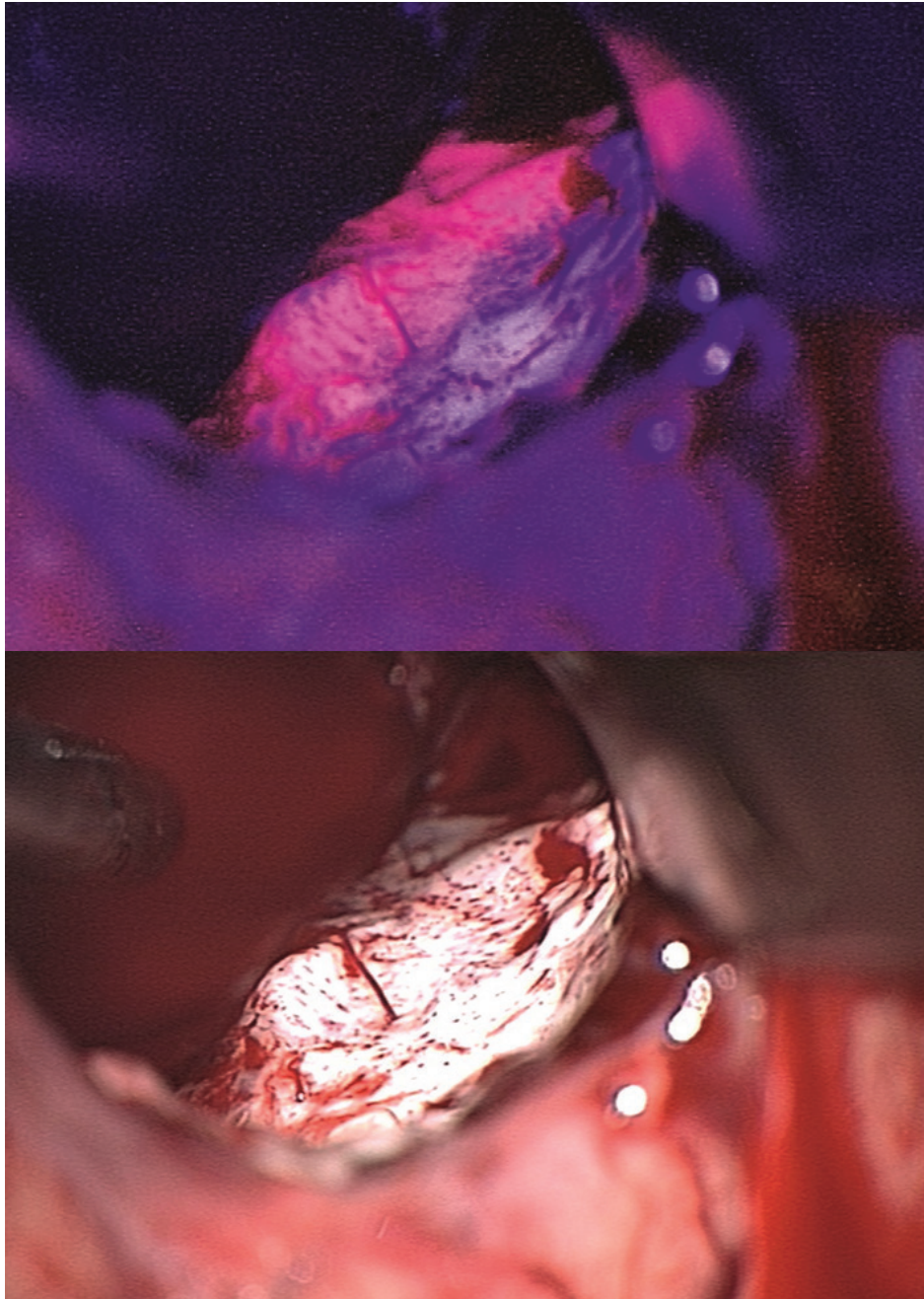
► **Figure 25.**
Photosensitiser being administered intravenously while patient photo-protects.



of time varying and depending on the photosensitiser used. Many of the photosensitisers used in the past were not specific enough and lasted in the body for a prolonged period. This meant the person was sensitive to light often for many weeks after the photosensitiser was given. They would therefore be required to undertake light protective measures, such as covering all areas of skin, wearing sunglasses and avoiding sunlight or bright indoor lights. The more modern photosensitisers have sought to overcome these limitations.

Getting light to the treatment area can be challenging but is essential as this allows accurate and specific treatment of the tumour and this is a highly researched area. In general, thin optical fibres, similar to those used in telecommunications, are used. These fibres are flexible and manoeuvrable allowing them to target difficult to reach areas. Light (normally from a laser) travels down the fibre and exits at the end, which is either placed inside the tumour or beside it. Several fibres can be used at the one time, which allows the treatment of larger tumours.

PDT has been researched for a wide range of different cancers, including head, neck and oral cancers, lung cancer, oesophagus (gullet) cancer, and pre-cancer (Barrett's oesophagus), prostate cancer and even glioblastoma (brain tumour). Some of the research has been in the form of clinical trials but the vast majority has been performed in laboratories. At the current time of publication, routine clinical PDT is rare for areas other than the skin. However the fluorescence (*red glow* - Figure 20) provided by the photosensitiser is routinely used as a guide for the removal of tumour tissue in the brain (glioblastoma - Figure 26) and has also been used for diagnosis of bladder cancer and pre-cancer. This technique is known as photodynamic diagnosis (PDD) rather than photodynamic therapy (PDT). ■



► **Figure 26.** Fluorescence of tumour tissue in the brain (top) and under normal white-light illumination (bottom). Image courtesy of medac GmbH.

Chapter 8:

Final words

Conclusion

In this Wee Discovery Book of PDT, we have given an overview of photodynamic therapy in the treatment of pre-cancerous sun damaged skin and non-invasive NMSC. We have introduced the skin and its structure, explaining how it can be damaged by radiation from the sun. This damage can result in a range of different skin pre-cancers and cancers and we have provided detailed information of the commonest conditions. Whilst there are many treatment options available for these pre-cancerous skin lesions and non-invasive NMSC this book focuses on PDT, as an effective and often patient preferred treatment. Significant side effects are rare and the biggest hurdle, pain, is no longer a notable issue due to the introduction of daylight PDT and low intensity irradiation.

PDT is an important tool amongst the available treatment options for these conditions. With a large variety of choices available, each

with their own advantages and disadvantages, it is possible to find the treatment that fits the patient best and to make changes when a treatment is not successful. Clinical research continues to see the advancement of PDT, improving how effective it is and exploring its use for cancers within the body. There is a lot of research across the globe investigating these important topics and we predict a bright future for this light-drug therapy.

It is vital that patients should be able to make an informed choice and as such there should be numerous sources of information available that vary in complexity. For healthcare professionals who are not specialist in skin diseases it is also important to have easily accessible information which can inform clinical practice. ■



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